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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|----------------------|
| 09/555,986 | 08/17/2000 | Gregor Cevc | 500.1011 | 9461 |
| 28089 | 7590 | 08/10/2006 | | EXAMINER |
| | | | | KISHORE, GOLLAMUDI S |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1615 | |

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|----------------------------|--------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/555,986 | CEVC, GREGOR |
| | Examiner | Art Unit |
| | Gollamudi S. Kishore, Ph.D | 1615 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 6-20-06.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 199,201,202,206-213 and 225-287 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 199,201,202,206-213 and 225-287 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

The RCE dated 6-20-06 is acknowledged.

Claims included in the prosecution are 199, 201, 202, 206-213 and 225-287.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 199, 201, 202, 206-213 and 225-287 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Line 2 of claim 199 stipulates that the composition comprises a **bilayer vesicle**.

According to line 6 however, the composition further contains a non-ionic detergent, which destabilizes the vesicle. This is contradictory to line 2. If the detergent destabilizes the vesicle, then how can one have a bilayer structure? Similar is the case with the other independent claims.

Claim 201 is confusing. What is meant by 'the surface of the vesicle carries a net electric charge and wherein the macromolecule carries a net electric charge and the net electric charge of the surface of the vesicle and the net electric charge of the macromolecule have the same sign? If the macromolecule is bound to the surface by charge interactions, then its net charge is neutralized. The terminology is very confusing.

It is unclear as to how one can consider a fatty acid as non-ionic detergent as recited in claim 206. A fatty acid is a negatively charged lipid.

Brij-type and Myrj-type in claim 207 and in some dependent claims renders these claims indefinite. Specific compounds with chemical names should be recited.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 199, 201-202, 206-208, 213, 225, 227, 229-230, 232, 235, 237, 240, 242-245, 250, 252-253, 257-258, 261, 263-268, 271-273, 278, 280-282 and 287 are rejected under 35 U.S.C. 102(b) as being anticipated by Weder (4,731,210).

Weder discloses compositions containing an amphipathic phospholipid, an amphipathic surfactant (cholic acid and salts) or a non-ionic surfactant (Tweens, Myrj, Brij, Peg sorbitan esters and others) and an active agent, which is a protein, an antigen, an antibody or a hormone (calcitonin and steroid hormones). The phospholipids include lecithin, phosphatidic acid and others. The process involves mixing the phospholipid and the solubilizing agent (sodium cholate) and adding the antibody, which

is absorbed on the surface of the liposome (abstract, col. 8, line 35 through col. 9, line 67, Examples and claims, claim 4 in particular).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that the systems disclosed by Weder are not based on a combination of bilayer-forming substances and solubilizing substances, but on the removal of the solubilizing agent, which leads to the desired compositions. These arguments are not persuasive. As pointed out before, first of all, applicant is incorrect in stating that the solubilizing agent is removed in Weder. Weder teaches the appropriate amounts of the lipid and the solubilizing agent for the formation of liposomes, which could be achieved by dilution or dialysis, or adding the appropriate amounts. In examples 3 and 5 on col. 14 the solubilizing agent is not removed at all. Secondly, instant claims are composition claims, though recited as product by process claims and applicant has not shown that the product of Weder is different from instant product. With regard to the process claims, first of all, instant claim language does not exclude the dilution of the solubilization agent. Secondly, as pointed out above, Weder teaches that a certain ratio of the lipid and solubilizing agents are necessary to obtain the liposomes. Applicant's arguments that Weder does not teach or suggest the association/adsorption of the pharmaceutical substances are not persuasive since in claim 4 Weder clearly teaches that the pharmaceutical substance is absorbed by incubating the liposome with one pharmaceutical substance just as in instant case.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 199, 201, 202, 206-213 and 225-287 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weder (4,731,210) by itself or in combination with WO 92/03122 cited above or vice versa.

As pointed out above, Weder discloses compositions containing an amphipathic phospholipid, an amphipathic surfactant (cholic acid and salts), a non-ionic surfactant (Brij, Myrj, Tweens, PEG sorbitan esters) and an active agent, which is a protein or a peptide or an antigen or antibody. The process involves mixing the phospholipid and the solubilizing agent (sodium cholate) and adding the antibody, which is absorbed on the surface of the liposome. Weder is also suggestive of incorporation of the active agent into the liposomes (abstract, col. 8, line 35 through col. 9, line 67, Examples and claims, claim 4 in particular). Weder does not specifically disclose claimed insulin or interleukin. However, since Weder provides guidance through examples as to how to absorb the active agent on the surface of the liposome and is suggestive of the applicability of the method to proteins, it would have been obvious to one of ordinary skill in the art to use claimed insulin or interleukin with a reasonable expectation of success.

WO discloses a composition containing two or more amphiphilic substances with different solubilities for the administration of various active substances including insulin. The first amphipathic substance is a phospholipid, the second amphipathic substance is sodium cholate and the third substance is insulin or an immunoglobulin or a hormone (note the abstract and entire publication, in particular, examples 140-142, 166 and claims of the English translation). Example 162 shows the addition of insulin and the mixture is left overnight.

One of ordinary skill in the art would be motivated further to use these active agents since the reference of WO which teaches similar compositions is suggestive of the feasibility of the use of insulin. Alternately, to adsorb insulin on the surface of liposomes of WO would have been obvious to one of ordinary skill in the art since Weder teaches in similar liposomes that the protein can either be absorbed or incorporated within the liposomes.

Applicant's arguments have been fully considered, but are not persuasive. Applicant once again argues that the solubilizing agent is removed in Weder and that Weder does not teach the association/absorption of the substance to the surface of the liposomes. These arguments have been addressed above. Applicant argues that WO 02 does not teach or suggest the association of the macromolecules with the outside of the surface of the vesicles. These arguments are not persuasive since WO is combined for its teachings of insulin and interleukin and as pointed out above, it would have been obvious to one of ordinary skill in the art to use these substances in Weder if compositions containing these active agents are desired.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 199, 201, 202, 206-213 and 225-287 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31, 38 and 70-76 of copending Application No. 09/621,574. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same compositions and the ratios of the lipid to the surfactant recited in the claims of said copending application fall within the generic terms in instant claims. The species of specific active agents recited in instant claims are deemed to be anticipated by the generic term, active agent in the claims of said copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the claims in 09/621,574 are directed to a preparation suitable for

transporting active agents through permeability barriers unlike the present claims.

These arguments are not persuasive since the claims recite the same components and method of preparation and the claims read on each other.

9. Claims 199, 201, 202, 206-213 and 225-287 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-66, 80-81, 88-100 of copending Application No. 10/357,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same compositions and instant species of active substances are deemed to be anticipated by the generic active ingredient recited in the claims of said patent. 'container', 'package' in which the compositions are placed as recited in claims 80, 81 and others recited in the copending application are deemed to be obvious forms for the composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the claims in the copending application are directed to preparation for application, administration or transport of an active ingredient into and through the pores in semi-permeable barriers or other constrictions and the preparation is in the form of mixed amphipathic aggregates with extended surfaces and formed from the combination of at least one first amphipathic component, at least one second amphipathic component (membrane destabilizing component) and at least one third (membrane destabilizing component) amphipathic component suspended in a suitable

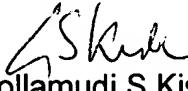
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liquid medium and the present claims are distinguishable over those in 10/357,618 and that the claims in said copending application do not teach or suggest a substrate in the form of a bilayer surface formed by at least one first surface-building amphipathic substance and at least one second surface-destabilizing amphipathic substance and molecules of at least one third amphipathic substance associated with the substrate. These arguments are not persuasive since just like in instant claims, the claims in said copending application requires three components, one is a phospholipid, the second is a surfactant and the third is an active substance and the composition is in the form of a bilayer structure. As evident from claims 64 and 67 of said copending application, the third substance is a hormone and the drug is mainly associated with the droplet surface. The claims read on each other, and the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK